Occupational Exposures and Female Breast Cancer Mortality in the United States

Kenneth P. Cantor, PhD
Patricia A. Stewart, PhD
Louise A. Brinton, PhD
Mustafa Dosemeci, PhD

Mortality records from 24 states, gathered from 1984 to 1989 and coded for occupation and industry, were used to develop leads to workplace exposures as possible breast cancer risk factors. A case-control approach was used, with separate analyses for blacks and whites. After excluding homemakers, 33,509 cases and 117,794 controls remained. A job exposure matrix was used to estimate the probability and level of 31 workplace exposures. After adjusting for socioeconomic status, suggestive associations for probability and level of exposure were found for styrene, several organic solvents (methylene chloride, carbon tetrachloride, formaldehyde), and several metals/metal oxides and acid mists. Because of the methodologic limitations of this study, its primary value is in suggesting hypotheses for further evaluation. The findings for styrene, selected solvents, and metals and metal-related exposures deserve additional study.

From the Environmental Epidemiology Branch, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland.

Address correspondence to: Kenneth P. Cantor, PhD, Environmental Epidemiology Branch, National Cancer Institute, 443 Executive Plaza North, Bethesda, MD 20892.

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Breast cancer is a major cause of death among US women and is now the second leading cause of cancer mortality. In 1993, there were an estimated 182,000 newly diagnosed cases of breast cancer among US women, and deaths were estimated at 46,000.[1] The lifetime risk of dying of breast cancer among US women was 3.60% in 1988–1990 (3.71% among whites and 3.48% among blacks).[1] The breast cancer mortality rate has increased slightly since 1973, from 26.9 to 27.5 per 100,000 in 1990 (all races). In contrast, incidence increased from 82.4 (1973) to 108.8 (1990) per 100,000.[1] It is the most common female cancer. The 1980–1987 increase in incidence, from 88.5 to 112.3 per 100,000, has been attributed in part to increases in early diagnosis and use of mammography.[2,3] Temporal changes in risk factors may also have contributed to the rise.[1]

Breast cancer etiology has been the subject of extensive epidemiologic investigation. Among established risk factors are reproductive, hormonal, and body shape characteristics, as well as ionizing radiation and family history[4,5]; however, these account for no more than 30% of incident cases.[4] Occupational exposures have received relatively little attention, possibly because the dominant etiologic paradigm involves factors related to hormonal status that, until recently, were considered to be largely absent from workplace settings and the general ambient environment.

Occupational studies may provide clues to fill in gaps in our under-

TABLE 1

Workplace Exposures Estimated for Probability and Level of Exposure in a Job-Exposure Matrix*

<u>1 Organic solvents</u>
2 Benzene
<u>3 Carbon tetrachloride</u>
<u>4 Methylene chloride</u>
5 Tetrachloroethylene
6 Trichloroethylene
<u>7 Styrene</u>
8 Butadiene
<u>9 Paints</u>
<u>10 Diesel and gasoline exhaust fumes</u>
<u>11 Polycyclic aromatic hydrocarbons</u>
12 Asphalt
<u>13 Metals and metal oxides (chromium, arsenic, beryllium, and nickel)</u>
<u>14 Lead/lead oxide</u>
<u>15 Cadmium</u>
<u>16 Solder</u>
17 Oils
<u>18 Polychlorinated biphenyls</u>
<u>19 Formaldehyde</u>
20 Asbestos
21 Talc
22 Silica (as quartz)
23 Wood dust
24 Paper dust
25 Aromatic amines
<u>26 Acid mists</u>
<u>27 Insecticides</u>
28 Herbicides
<u>29 Radiofrequency radiation</u>
30 Microwave radiation
<u>31 Ionizing radiation</u>

* Odds ratios for probability and level of exposure to underlined items are shown in Tables 3 through 7.

standing of breast cancer etiology. Among exposures suggested as occupational risk factors are organochlorine pesticides and other chemicals commonly found in the workplace and general environment,[6] electromagnetic fields,[7–9] ionizing radiation,[10] and cadmium.[11] There are few direct epidemiologic data about specific exposures. Studies have suggested a possible link with asbestos,[12] as well as with isopropyl alcohol, freon, solder flux, and methylene chloride[13]; however, these findings are based on small numbers of exposed cases. Other exposures warrant evaluation. Where occupational titles have been evaluated, elevated risk has been associated with employment as a manager, teacher, government worker, and administrative or clerical worker.[14–16] A positive risk gradient has been found with social class as imputed from occupation[17,18] and with occupations with low levels of physical activity.[15]

To seek further clues to breast cancer etiology, we have analyzed data from a large database of mortality records from 24 states for the years 1984–1989 that had been coded for occupation and industry. The breast cancer mortality data from this source also have been used by Rubin et al[19] to identify occupational groups at high risk for breast cancer for the purpose of establishing screening priorities.

Methods

Since 1984, the National Cancer Institute, the National Institute for Occupational Safety and Health (NIOSH), and the National Center for Health Statistics have supported the coding of usual occupation and industry listed on death certificates from selected states. Records from 1984–1989 form the database from which cases and controls were selected for this study. The full data set includes over 2.5 million records from 24 states (CO, GA, ID, IN, KA, KY, ME, MO, NE, NV, NH, NJ, NM, NC, OH, OK, RI, SC, TN, UT, WA, WV, WI, VT).

Cases for this analysis were white and black women whose death certificate listed breast cancer as the underlying cause of death (International Classification of Diseases, 9th Revision, Code 174). Four controls per case were randomly selected from all noncancer deaths and frequency matched for age (in 5-year groups), gender, and race. A total of 59,515 women died of breast cancer as the underlying cause. Black women accounted for 5,970 of these (10.0%). Usual occupation and industry were coded by trained individuals using three-digit US rubrics published in the US Census for 1980.[20] A total of 24,148 (45.1%) white cases and 110,067 (51.7%) white controls were coded as homemakers, as were 1,858 (31.1%) black cases and 9,041 (37.9%) black controls. After excluding these individuals, the analysis database numbered 29,397 white cases, 102,955 white controls, 4,112 black cases, and 14,839 black controls.

TABLE 2

Characteristics of Breast Cancer Deaths, by Race

Characteristic	Whites	Blacks
Age at death		
<30	171	49
30–39	2,108	495
40–49	5,340	928
50–59	9,235	1,203
60–69	13,941	1,419
70–79	12,959	1,128
80+	9,791	748
Total	53,545	5,970
Socioeconomic status (from occupation)		
Low	6,681	2,112
Middle	43,637 (19,489)*	3,654 (1,796)*
High	3,227	204
Homemaker as occupation?		
Yes	24,148	1,858
No	29,397	4,112

* Numbers in parentheses represent those remaining in the analysis after removal of homemakers from the database.

TABLE 3
Breast Cancer Among White Women, by Exposure Probability

Exposure Category	Exposure Probability (0–4)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Organic solvents	0	20,390	66,367	1.00	1.00	
	1	2,229	8,303	0.87‡	1.00	0.95–1.1
	2	3,511	14,158	0.81‡	1.02	0.97–1.1
	3	1,479	6,841	0.70‡	1.09‡	1.0–1.2
	4	1,336	5,398	0.81‡	1.01	0.95–1.1
Carbon tetrachloride	0	21,746	71,932	1.00	1.00	
	1	4,907	18,892	0.86‡	0.98	0.9–1.0
	2	2,138	9,532	0.74‡	1.13‡	1.1–1.2
	3	161	694	0.77‡	1.16	0.97–1.4
	4	5	37	0.44	0.75	0.3–2.0
Methylene chloride	0	20,510	66,694	1.00	1.00	
	1	5,119	20,398	0.82‡	0.94‡	0.9–0.98
	2	2,358	10,418	0.73‡	1.15‡	1.1–1.2
	3	945	3,475	0.89‡	1.05	0.97–1.1
	4	5	37	0.44	0.76	0.3–2.0
Styrene	0	27,610	96,272	1.00	1.00	
	1	804	2,722	1.03	1.13‡	1.0–1.2
	2	527	2,021	0.91	1.18‡	1.1–1.3
	3	64	212	1.05	1.38‡	1.0–1.9
	4	4	27	—	—	
Paints	0	28,208	98,311	1.00	1.00	
	1	391	1,233	1.10	1.16‡	1.0–1.3
	2	289	1,205	0.84	1.07	0.9–1.2
	3	137	591	0.81	1.13	0.9–1.4
	4	16	45	1.24	1.80	0.97–3.3
Diesel and gasoline exhaust fumes	0	26,449	90,562	1.00	1.00	
	1	701	2,246	1.07	1.06	0.97–1.2
	2	444	1,476	1.03	1.08	0.97–1.2
	3	278	920	1.04	1.12	0.97–1.3
	4	1,162	6,143	0.65‡	0.92‡	0.9–0.98
Polycyclic aromatic hydrocarbons	0	24,123	79,906	1.00	1.00	
	1	2,063	7,128	0.96	0.88‡	0.8–0.9
	2	142	623	0.75	1.00	0.8–1.2
	3	1,717	8,553	0.66‡	0.74‡	0.7–0.8
	4	1,011	5,210	0.64‡	0.96	0.9–1.03
Metals and metal oxides	0	26,791	93,184	1.00	1.00	
	1	1,079	3,526	1.06	1.13‡	1.0–1.2
	2	474	1,871	0.88‡	1.12‡	1.0–1.3
	3	624	2,554	0.85‡	1.11‡	1.0–1.2
	4	3	6	—	—	
Lead/lead oxide	0	26,696	92,943	1.00	1.00	
	1	1,177	3,998	1.02	1.13‡	1.1–1.2
	2	512	2,017	0.88	1.05	0.9–1.2
	3	574	2,157	0.92	1.16‡	1.1–1.3
	4	3	6	—	—	
Cadmium	0	27,781	96,528	1.00	1.00	
	1	776	2,869	0.94	1.05	0.97–1.1
	2	377	1,412	0.92	1.13‡	1.0–1.3
	3	125	566	0.77‡	1.07	0.9–1.3
Solder	0	27,908	97,044	1.00	1.00	
	1	582	1,999	1.01	1.07	0.97–1.2
	2	451	1,803	0.87	1.09	0.98–1.2
	3	109	525	0.72	1.00	0.8–1.2
	4	11	19	1.99	2.97‡	1.3–6.6

TABLE 3—*Continued*

Exposure Category	Exposure Probability (0–4)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Polychlorinated biphenyls	0	28,623	99,650	1.00	1.00	
	1	314	1,257	0.87‡	1.03	0.9–1.2
	2	129	564	0.79‡	1.09	0.9–1.3
	3	14	42	1.16	1.28	0.7–2.4
Formaldehyde	0	20,237	65,813	1.00	1.00	
	1	5,119	20,597	0.81‡	0.95‡	0.92–0.99
	2	1,173	4,809	0.79‡	1.06	0.99–1.1
	3	2,377	9,719	0.79‡	1.06‡	1.0–1.1
	4	15	52	0.94	1.03	0.6–1.9
Asbestos	0	26,478	90,774	1.00	1.00	
	1	2,023	8,459	0.82‡	1.06‡	1.0–1.1
	2	364	1,400	0.89	1.14‡	1.0–1.3
	3	123	565	0.75‡	1.03	0.8–1.3
	4	2	9	—	—	
Acid mists	0	22,098	73,374	1.00	1.00	
	1	4,836	18,971	0.85‡	0.92‡	0.89–0.96
	2	1,456	6,716	0.72‡	1.07‡	1.0–1.1
	3	530	1,908	0.92	1.15‡	1.0–1.3
	4	40	153	0.86	1.15	0.8–1.7
Insecticides	0	28,939	100,919	1.00	1.00	
	1	33	91	1.27	1.13	0.7–1.7
	2	19	73	0.91	1.20	0.7–2.0
	3	110	493	0.78‡	1.07	0.9–1.3
Radiofrequency electromagnetic fields	0	24,505	84,484	1.00	1.00	
	1	2,107	6,939	1.05	1.00	0.9–1.1
	2	668	2,630	0.87‡	1.06	0.97–1.2
	3	1,518	6,484	0.81‡	1.15‡	1.1–1.2
	4	199	699	0.99	0.99	0.8–1.2
Ionizing radiation	0	26,029	89,471	1.00	1.00	
	1	1,227	4,978	0.85‡	0.92‡	0.86–0.98
	2	107	389	0.94	1.14	0.9–1.4
	3	112	354	1.09	1.09	0.9–1.4
	4	1,581	6,204	0.88‡	0.87‡	0.8–0.9

* Adjusted for age (at death) only.
† Adjusted for age and socioeconomic status (as imputed from occupation).
‡ 95% confidence interval excludes 1.00.

Occupation and industry codes were linked with other information to estimate exposures using a job exposure matrix developed for this study by one of the authors (PAS). We estimated the probability and level of exposure for each of 31 occupational exposures that either have been suggested as risk factors for breast cancer or are common toxins in occupational settings (Table 1). The job exposure matrix for this study was based on the professional judgment of an industrial hygienist, supplemented by the general occupational hygiene literature and two databases: NIOSH's Job Exposure Matrix[21] and the Integrated Management Information System of the Occupational Safety and Health Administration.[22] Probability of exposure was assigned on a scale of 0 to 4 and level of exposure on a scale of 0 to 3. The probability and level of exposure associated with the scores varied by exposure; thus, a probability score of 2 for an exposure was not equivalent to the same score for another. Each unique combination of job and industry listed on mortality records was assigned a probability and level score for each exposure, based on a modification of an approach described by Dosemeci et al.[23]

The relative risk for increasing probability or level of exposure to each of the 31 occupational factors (relative to the nonexposed) was estimated by the odds ratio, using the method of Gart.[24] Analyses were adjusted for age at death (<49, 50–59, 60+) and, in some analyses, for socioeconomic class derived from the occupational title (three levels). Analyses were race specific (whites and blacks).

Results

Table 1 lists the 31 workplace exposures we evaluated. For presentation (Tables 3 through 7), we se-

TABLE 4
Breast Cancer Among White Women, by Exposure Level

Exposure Category	Exposure Level (0–3)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)‡	95% Confidence Intervals
Organic solvents	0	20,390	66,367	1.00	1.00	
	1	6,113	24,607	0.81‡	0.98	0.95–1.0
	2	1,231	4,464	0.90‡	1.05	0.98–1.1
	3	1,211	5,629	0.70‡	1.10‡	1.0–1.2
Carbon tetrachloride	0	21,746	71,932	1.00	1.00	
	1	5,774	23,422	0.82‡	0.98	0.95–1.0
	2	837	3,102	0.89‡	1.15‡	1.1–1.3
	3	600	2,631	0.75‡	1.21‡	1.1–1.3
Methylene chloride	0	20,510	66,694	1.00	1.00	
	1	5,416	21,936	0.80‡	0.95‡	0.9–0.98
	2	1,298	4,875	0.87‡	1.04	0.97–1.1
	3	1,713	7,517	0.74‡	1.17‡	1.1–1.3
Styrene	0	27,610	96,272	1.00	1.00	
	1	807	2,763	1.02	1.16‡	1.1–1.3
	2	522	1,938	0.94	1.13‡	1.0–1.3
	3	70	281	0.87	1.19	0.9–1.6
Paints	0	28,208	98,311	1.00	1.00	
	1	505	1,692	1.04	1.18‡	1.1–1.3
	2	205	911	0.78	1.05	0.9–1.2
	3	123	471	0.91	1.09	0.9–1.3
Diesel and gasoline exhaust fumes	0	26,449	90,562	1.00	1.00	
	1	1,938	8,571	0.77	0.98	0.9–1.0
	2	340	901	1.29	1.18‡	1.0–1.4
	3	307	1,313	0.80	0.93	0.8–1.1
Polycyclic aromatic hydrocarbons	0	24,123	79,906	1.00	1.00	
	1	1,769	8,105	0.72‡	0.88‡	0.8–0.9
	2	1,438	7,072	0.67‡	0.77‡	0.7–0.8
	3	1,726	6,337	0.90‡	0.86‡	0.8–0.9
Metals and metal oxides	0	26,791	93,184	1.00	1.00	
	1	1,483	5,256	0.98	1.13‡	1.1–1.2
	2	269	938	0.99	1.05	0.9–1.2
	3	428	1,763	0.84‡	1.14‡	1.0–1.3
Lead/lead oxide	0	26,696	92,943	1.00	1.00	
	1	1,467	5,131	0.99	1.12‡	1.1–1.2
	2	619	2,379	0.90‡	1.11‡	1.0–1.2
	3	180	668	0.93	1.09	0.9–1.3
Cadmium	0	27,781	96,528	1.00	1.00	
	1	889	3,317	0.93	1.08‡	1.0–1.2
	2	258	1,045	0.86‡	1.08	0.9–1.3
	3	131	485	0.93	1.05	0.9–1.3
Solder	0	27,908	97,044	1.00	1.00	
	1	834	3,060	0.95	1.09‡	1.0–1.2
	2	219	919	0.83	0.96	0.8–1.1
	3	100	367	0.94	1.22	0.97–1.5
Polychlorinated biphenyls	0	28,623	99,650	1.00	1.00	
	1	360	1,502	0.84	1.03	0.9–1.2
	2	93	359	0.90	1.12	0.9–1.4
	3	4	2	—	—	
Formaldehyde	0	20,237	65,813	1.00	1.00	
	1	5,464	21,705	0.82	0.96‡	0.93–0.99
	2	1,405	5,860	0.78	0.93‡	0.9–0.99
	3	1,815	7,612	0.77	1.19‡	1.1–1.3

TABLE 4—*Continued*

Exposure Category	Exposure Level (0–3)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)‡	95% Confidence Intervals
Asbestos	0	26,478	90,774	1.00	1.00	
	1	1,668	6,627	0.86‡	1.08‡	1.0–1.2
	2	360	1,931	0.64‡	0.94	0.8–1.1
	3	484	1,875	0.88‡	1.12‡	1.0–1.3
Acid mists	0	22,098	73,374	1.00	1.00	
	1	5,358	22,055	0.81‡	0.94‡	0.9–0.97
	2	832	3,051	0.91‡	0.95	0.9–1.0
	3	672	2,642	0.84‡	1.15‡	1.1–1.3
Insecticides	0	28,939	100,919	1.00	1.00	
	1	41	111	1.29	1.19	0.8–1.7
	2	118	532	0.78‡	1.07	0.9–1.3
	3	3	14	—	—	
Radiofrequency electromagnetic fields	0	24,505	84,484	1.00	1.00	
	1	1,183	4,260	0.96	1.15‡	1.1–1.2
	2	1,940	6,758	0.99	0.95	0.9–1.0
	3	1,369	5,734	0.82‡	1.14‡	1.1–1.2
Ionizing radiation	0	26,029	89,471	1.00	1.00	
	1	831	3,677	0.78‡	0.93	0.9–1.0
	2	614	2,035	1.04	0.96	0.9–1.1
	3	1,582	6,213	0.87‡	0.87‡	0.8–0.9

* Adjusted for age (at death) only.
† Adjusted for age and socioeconomic status (as imputed from occupation).
‡ 95% confidence interval excludes 1.00.

lected 18 of these, based on hypothesized elevated risk in the literature, observation in this study of an association, or a high prevalence of exposure in the general population.

Table 2 shows the different age distributions of breast cancer deaths among whites and blacks. Among white women, 14.2% of breast cancer deaths were under age 50 and 42.5% were 70 years old or older, whereas among blacks, 24.7% were less than age 50 and 31.4% were 70 or older. These data do not reveal whether the younger average age at death among blacks reflects the age structure of the underlying population, or different age-specific rates between the races, or both. Also shown in Table 2 are the distribution of socioeconomic status (as implied by usual occupation), and whether "homemaker" or equivalent was listed on the death certificate.

Tables 3 through 7 show results for the 18 exposures highlighted in Table 1. Tables 3 and 4 show results among whites for exposure probability and exposure level, and Tables 5 and 6 show results among blacks. Odds ratios (ORs) are shown with adjustment by age only (OR(1)) and with adjustment by age and by SES (OR(2)). The further adjustment by SES generally resulted in OR estimates larger than estimates adjusted for age alone. SES has been found to be linked to breast cancer risk; the increase in observed risk with SES adjustment likely reflects higher probability and level of exposure to most substances among persons with occupations at the lower end of the SES scale. Table 7 presents ORs for level of exposure before (columns 1 and 3) and after (columns 2 and 4) removal of subjects with a low probability of exposure to the listed items. The results in columns 1 and 3 are from Tables 4 (whites) and 6 (blacks) and are included in Table 7 for ease of comparison.

We found little or no evidence of association for several of the exposures highlighted in Table 1: diesel and gasoline exhaust fumes, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and insecticides. For PAHs, the ORs for both probability and level of exposure among whites and blacks were consistently less than 1.0, as they were for insecticide exposure among blacks.

ORs for exposure to the grouped organic solvents were not remarkable; however, there was evidence for associations with some specific solvents, namely carbon tetrachloride (exposure level and probability among whites); methylene chloride (exposure level among whites and blacks); and formaldehyde (exposure level among whites and blacks; exposure probability in blacks).

Styrene showed the most consistent evidence for an association with breast cancer mortality, with elevated ORs among both race groups for the level and probability of exposure. The OR for exposure level to styrene increased after persons who had a low probability of exposure

TABLE 5
Breast Cancer Among Black Women, by Exposure Probability

Exposure Category	Exposure Probability (0–4)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Organic solvents	0	2,020	6,578	1.00	1.00	
	1	272	808	1.09	1.20‡	1.0–1.4
	2	504	1,722	0.95	1.16‡	1.0–1.3
	3	963	4,173	0.74‡	1.01	0.9–1.1
	4	305	1,369	0.73‡	0.91	0.8–1.1
Carbon tetrachloride	0	2,180	7,086	1.00	1.00	
	1	744	2,663	0.90‡	1.06	0.95–1.2
	2	1,050	4,495	0.75‡	0.99	0.9–1.1
	3	88	402	0.71‡	0.94	0.7–1.2
	4	2	6	—	—	—
Methylene chloride	0	2,041	6,697	1.00	1.00	
	1	752	2,642	0.93	1.09	0.98–1.2
	2	1,127	4,864	0.75‡	1.02	0.9–1.1
	3	141	441	1.04	1.13	0.9–1.4
	4	2	6	—	—	—
Styrene	0	3,918	14,284	1.00	1.00	
	1	80	193	1.50‡	1.49‡	1.1–2.0
	2	61	166	1.34	1.52‡	1.1–2.1
	3	7	22	1.16	1.32	0.5–3.3
	4	2	3	—	—	—
Paints	0	3,911	13,949	1.00	1.00	
	1	38	80	1.68	1.74‡	1.2–2.6
	2	99	590	0.60	0.70‡	0.6–0.9
	3	18	48	1.33	1.62	0.9–2.9
	4	4	8	—	—	
Diesel and gasoline exhaust fumes	0	2,917	9,565	1.00	1.00	
	1	62	142	1.42‡	1.46‡	1.1–2.0
	2	46	135	1.12	1.27	0.9–1.8
	3	33	123	0.87	0.87	0.6–1.3
	4	1,007	4,709	0.70‡	0.84‡	0.8–0.9
Polycyclic aromatic hydrocarbons	0	2,554	8,339	1.00	1.00	
	1	218	672	1.06	0.89	0.8–1.1
	2	24	93	0.83	0.99	0.6–1.6
	3	355	1,431	0.80‡	0.71‡	0.6–0.8
	4	921	4,144	0.72‡	0.93	0.8–1.0
Metals and metal oxides	0	3,849	14,096	1.00	1.00	
	1	109	252	1.57‡	1.58‡	1.3–2.0
	2	53	179	1.08	1.22	0.9–1.7
	3	55	131	1.53‡	1.75‡	1.3–2.4
	4	0	1	—	—	
Lead/lead oxide	0	3,815	14,031	1.00	1.00	
	1	132	302	1.60‡	1.71‡	1.4–2.1
	2	60	197	1.12	1.18	0.9–1.6
	3	58	127	1.67‡	1.86‡	1.3–2.6
	4	0	1	—	—	—
Cadmium	0	3,862	13,833	1.00	1.00	
	1	153	721	0.76‡	0.86	0.7–1.0
	2	35	89	1.41	1.53‡	1.0–2.3
	3	20	38	1.87‡	2.32‡	1.3–4.1
Solder	0	3,882	13,869	1.00	1.00	
	1	63	178	1.26	1.30	0.96–1.8
	2	108	600	0.65‡	0.75‡	0.6–0.9
	3	17	31	1.95‡	2.40‡	1.3–4.5
Polychlorinated biphenyls	0	3,954	14,046	1.00	1.00	
	1	100	575	0.62‡	0.72‡	0.6–0.9
	2	20	62	1.15	1.37	0.8–2.3

TABLE 5—*Continued*

Exposure Category	Exposure Probability (0–4)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Formaldehyde	0	2,085	7,137	1.00	1.00	
	1	1,458	5,874	0.84‡	1.11‡	1.0–1.2
	2	206	758	0.93	1.16	0.98–1.4
	3	311	865	1.22‡	1.45‡	1.2–1.7
	4	4	12	—	—	
Asbestos	0	3,751	13,791	1.00	1.00	
	1	248	653	1.39‡	1.68‡	1.4–2.0
	2	48	160	1.10	1.26	0.9–1.8
	3	18	60	1.10	1.32	0.8–2.3
	4	1	0	—	—	
Acid mists	0	2,293	7,707	1.00	1.00	
	1	1,427	5,649	0.85‡	1.01	0.9–1.1
	2	290	1,162	0.83‡	1.10	0.9–1.3
	3	50	134	1.24	1.43‡	1.0–2.0
	4	6	7	2.89	3.62‡	1.1–12.0
Insecticides	0	4,030	14,384	1.00	1.00	
	1	3	10	—	—	
	2	2	14	—	—	
	3	39	284	0.50‡	0.57‡	0.4–0.8
Radiofrequency electromagnetic fields	0	3,437	12,596	1.00	1.00	
	1	28	585	1.42‡	1.22‡	1.0–1.4
	2	92	409	0.83	0.93	0.7–1.2
	3	274	965	1.04	1.27‡	1.1–1.5
	4	35	115	1.13	1.08	0.7–1.6
Ionizing radiation	0	3,594	13,068	1.00	1.00	
	1	202	714	1.02	1.04	0.9–1.2
	2	18	51	1.28	1.26	0.8–2.2
	3	10	18	1.99	1.80	0.9–4.5
	4	242	817	1.07	1.02	0.9–1.2

* Adjusted for age (at death) only.
† Adjusted for age and socioeconomic status (as imputed from occupation).
‡ 95% confidence interval excludes 1.00.

were removed from the analysis (Table 7).

Elevated risk was also linked to some metal exposures: a combined group that included chromium, arsenic, beryllium, and nickel (level and probability of exposure among whites and blacks); lead/lead oxide (exposure probability for whites, exposure level among blacks); and cadmium (probability and level of exposure among blacks). The findings for exposure to solder were mixed, with blacks, but not whites, showing elevated risk (especially for exposure probability). Acid mists, often found in metalworking occupational environments, showed an association with exposure level in both races.

Asbestos exposure was weakly linked to breast cancer mortality in these data, as were exposures to nonionizing radiofrequency radiation and ionizing radiation.

Discussion

Breast cancer incidence and mortality rates show remarkable international variation,[25] little of which is explained by known risk factors. This variation and recent suggestions of risk from environmental factors[6] have motivated us to look beyond the usual array of (mostly) hormonally associated factors to evaluate selected workplace exposures. Consistency in positive associations for some exposures here should be considered as clues to identify candidates for more precise evaluation in further studies. An efficient and convenient approach for this effort is to analyze available data in crude analyses for first-level evaluations of many exposures. We therefore used a recently developed database of mortality records, with coded occupation and industry, and a job exposure matrix approach for approximating exposures.

Our findings must be evaluated in the context of the study's methodologic limitations. If a link truly exists with one or more of the factors that we evaluated, the association might easily have been missed. We therefore do not place much emphasis on our negative findings. Our inability to control for most of the recognized breast cancer risk factors raises the possibility of false elevations of risk for some exposures. These weaknesses were due to vari-

TABLE 6
Breast Cancer Among Black Women, by Exposure Level

Exposure Category	Exposure Level (0–3)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Organic solvents	0	2,020	6,578	1.00	1.00	
	1	1,664	6,776	0.80	1.03	0.9–1.1
	2	189	568	1.00	1.20‡	1.0–1.4
	3	191	728	0.85	1.18	0.97–1.4
Carbon tetrachloride	0	2,180	7,086	1.00	1.00	
	1	1,626	6,627	0.80‡	1.00	0.9–1.1
	2	125	389	1.04	1.32‡	1.1–1.6
	3	133	550	0.79‡	1.07	0.9–1.3
Methylene chloride	0	2,041	6,697	1.00	1.00	
	1	1,552	6,408	0.79‡	1.01	0.9–1.1
	2	238	823	0.94	1.12	0.9–1.3
	3	232	722	1.05	1.46‡	1.2–1.7
Styrene	0	3,918	14,284	1.00	1.00	
	1	87	204	1.54‡	1.59‡	1.2–2.1
	2	63	180	1.27	1.41‡	1.0–1.9
Paints	0	3,911	13,949	1.00	1.00	
	1	90	333	0.97	1.09	0.9–1.4
	2	69	393	0.63‡	0.73	0.6–0.95
Diesel and gasoline exhaust fumes	0	2,917	9,565	1.00	1.00	
	1	1,084	4,905	0.72‡	0.87‡	0.8–0.96
	2	17	44	1.26	1.16	0.6–2.1
	3	47	160	0.97	1.06	0.8–1.5
Polycyclic aromatic hydrocarbons	0	2,554	8,339	1.00	1.00	
	1	1,006	4,495	0.73‡	0.89‡	0.8–0.98
	2	246	935	0.85‡	0.78‡	0.7–0.9
	3	266	910	0.95	0.80‡	0.7–0.9
Metals and metal oxides	0	3,849	14,096	1.00	1.00	
	1	131	340	1.40‡	1.47‡	1.2–1.8
	2	28	61	1.66‡	1.65‡	1.0–2.7
	3	58	162	1.31	1.54‡	1.1–2.1
Lead/lead oxide	0	3,815	14,031	1.00	1.00	
	1	164	399	1.50‡	1.57‡	1.3–1.9
	2	86	228	1.38‡	1.55‡	1.2–2.0
Cadmium	0	3,862	13,833	1.00	1.00	
	1	163	722	0.81‡	0.92	0.8–1.1
	2	45	126	1.28	1.42	0.99–2.0
Solder	0	3,882	13,869	1.00	1.00	
	1	153	700	0.79‡	0.89	0.7–1.1
	2	35	109	1.15	1.26	0.8–1.9
Polychlorinated biphenyls	0	3,954	14,046	1.00	1.00	
	1	108	591	0.65‡	0.76‡	0.6–0.9
	2	12	49	0.88	0.98	0.5–1.9
Formaldehyde	0	2,085	7,137	1.00	1.00	
	1	1,478	5,840	0.86	1.11‡	1.0–1.2
	2	309	940	1.12	1.31‡	1.1–1.5
	3	192	729	0.90	1.26‡	1.0–1.5
Asbestos	0	3,751	13,791	1.00	1.00	
	1	230	615	1.37‡	1.64‡	1.4–1.9
	2	30	80	1.38	1.79‡	1.1–2.8
	3	55	178	1.14	1.31	0.95–1.8
Acid mists	0	2,293	7,707	1.00	1.00	
	1	1,589	6,421	0.83	1.02	0.9–1.1
	2	70	223	1.05	0.92	0.7–1.2
	3	114	308	1.24	1.50‡	1.2–1.9

TABLE 6—*Continued*

Exposure Category	Exposure Probability (0–4)	Cases	Controls	Odds Ratio (1)*	Odds Ratio (2)†	95% Confidence Intervals
Insecticides	0	4,030	14,384	1.00	1.00	
	1	44	308	0.52‡	0.58‡	0.4–0.8
Radiofrequency electromagnetic fields	0	3,437	12,596	1.00	1.00	
	1	150	487	1.13	1.23‡	1.0–1.5
	2	243	815	1.09	1.02	0.8–1.2
	3	236	772	1.12	1.34‡	1.1–1.5
Ionizing radiation	0	3,594	13,068	1.00	1.00	
	1	151	584	0.93	1.01	0.8–1.2
	2	79	198	1.44‡	1.22	0.9–1.6
	3	242	818	1.06	1.02	0.9–1.2

* Adjusted for age (at death) only.
† Adjusted for age and socioeconomic status (as imputed from occupation).
‡ 95% confidence interval excludes 1.00.

ous aspects of the methodologic approach, including use of the death certificate as a primary source of information and application of a job exposure matrix for exposure estimates.

Coding of cause of death on mortality records has been shown to be accurate for breast cancer decedents.[26] However, if case-fatality rates varied among women with different occupational exposures, our estimates of breast cancer risk would be biased. Additionally, a likely source of bias arose from misclassification of exposure that was based on the death certificate entry of "usual occupation" and "usual industry." Many employed persons, especially women in the age ranges that predominated in this study, have held a variety of occupational positions, and selection of the occupation entered on the death certificate was possibly biased in favor of the most recent job or the occupation reflecting the highest socioeconomic level. The years when exposure occurred were unknown, so that assessments of exposure probability and level ignored duration and latency considerations, further limiting interpretation of our findings.

The death certificate does not include information on most known (or suspected) risk factors for breast cancer, such as age at menarche, age at first birth, age at menopause, history of benign breast disease, height, alcohol consumption, other dietary factors, and family history of breast cancer.[5] We were therefore not able to directly control for these factors in the analysis. However, we did exercise limited control over some of these factors by adjusting for SES (as inferred from usual occupation). Breast cancer risk has been observed to be linked with SES,[17,18] most likely through secondary links to hormonal or dietary factors.

The use of a job exposure matrix to estimate workplace exposures has the great strength of combining similar exposures that occur in disparate occupational settings.[27,28] Its limitations include loss of statistical power (when compared to more precise methods of estimating exposures), enhancement of confounding from overlapping exposures, and errors in the precision and accuracy of risk estimates that arise from unavoidable and extensive exposure misclassification.[27,29,30]

ORs for the 18 workplace exposures shown in Tables 3 through 7 were selected from among the 31 evaluated. The selection was based on information in the literature that suggested elevated risk, observation within this study of an association, or the prevalence of the exposure among the general population. In the context of these limitations, it is necessary to apply a flexible approach in deciding which exposures may pose a risk of breast cancer.

The most consistent finding of risk for any single exposure category was for styrene. Elevated risk was found for both probability and level of styrene exposure in blacks and whites. However, no excess in breast cancer mortality has been observed among cohorts of female rubber production workers with a potential for styrene exposure.[31–34]

Several exposure groupings of metals exhibited rather consistent associations for level and/or probability of exposure. Excess risks were seen for level or probability of exposure among either blacks or whites for lead, cadmium, solder, acid mists (an exposure common in several metalworking occupations), and a combined grouping that included chromium, arsenic, beryllium, and nickel. It is likely that many of these exposures were overlapping and any underlying causal associations were probably related to only one or a very few of them. As with most of the exposures we evaluated, relatively little information has been published that addresses metals and breast cancer risk. In a cohort study of workers in an aircraft maintenance facility, women exposed to solder were at excess breast cancer risk.[13]

TABLE 7
Breast Cancer by Exposure Level* Among White and Black Women, for (1) All Probability Levels of Exposure and (2) Excluding Women with Low Probability of Exposure

Exposure Category	Exposure Level (0–3)	Whites Odds Ratio (1)†	Whites Odds Ratio (2)‡	Blacks Odds Ratio (1)†	Blacks Odds Ratio (2)‡
Organic solvents	0	1.00	1.00	1.00	1.00
	1	0.98	1.01	1.03	1.00
	2	1.05	1.04	1.20§	1.20§
	3	1.10§	1.10§	1.18	1.17
Carbon tetrachloride	0	1.00	1.00	1.00	1.00
	1	0.98	1.11§	1.00	0.95
	2	1.15§	1.16§	1.32§	1.24
	3	1.21§	1.23§	1.07	0.96
Methylene chloride	0	1.00	1.00	1.00	1.00
	1	0.95	1.12§	1.01	0.98
	2	1.04	1.04	1.12	1.08
	3	1.17§	1.28§	1.46§	1.21
Styrene	0	1.00	1.00	1.00	1.00
	1	1.16§	1.21§	1.59§	2.14§
	2	1.13§	1.18§	1.41§	1.36
	3	1.19	1.20		
Paints	0	1.00	1.00	1.00	1.00
	1	1.18§	1.26	1.09	0.84
	2	1.05	1.02	0.73	0.74
	3	1.09	1.09		
Diesel and gasoline exhaust fumes	0	1.00	1.00	1.00	1.00
	1	0.98	0.96	0.87§	0.84
	2	1.18§	1.18	1.16	1.27
	3	0.93	0.90	1.06	1.00
Polycyclic aromatic hydrocarbons	0	1.00	1.00	1.00	1.00
	1	0.88§	0.95	0.89§	0.92
	2	0.77§	0.76§	0.78§	0.77§
	3	0.86§	0.75§	0.80§	0.66§
Metals and metal oxides	0	1.00	1.00	1.00	1.00
	1	1.13§	1.15§	1.47§	1.38
	2	1.05	1.06	1.65§	1.82§
	3	1.14§	1.12	1.54§	1.36
Lead/lead oxide	0	1.00	1.00	1.00	1.00
	1	1.12§	1.11	1.57§	1.34
	2	1.11§	1.11§	1.55§	1.51§
	3	1.09	1.08		
Cadmium	0	1.00	1.00	1.00	1.00
	1	1.08§	1.21§	0.92	2.30§
	2	1.08	1.08	1.42	1.51
	3	1.05	1.03		
Solder	0	1.00	1.00	1.00	1.00
	1	1.09§	1.16§	0.89	0.72
	2	0.96	0.96	1.26	1.47
	3	1.22	1.22		
Polychlorinated biphenyls	0	1.00	1.00	1.00	1.00
	1	1.03	1.00	0.76§	2.01
	2	1.12	1.20	0.98	0.91
	3	—			
Formaldehyde	0	1.00	1.00	1.00	1.00
	1	0.96§	1.14§	1.11§	1.38§
	2	0.93§	0.93	1.31§	1.30§
	3	1.19§	1.20§	1.26§	1.36§

TABLE 7—*Continued*

Exposure Category	Exposure Level (0–3)	Whites		Blacks	
		Odds Ratio (1)†	Odds Ratio (2)‡	Odds Ratio (1)†	Odds Ratio (2)‡
Asbestos	0	1.00	1.00	1.00	1.00
	1	1.08§	1.10	1.64§	1.60
	2	0.94	1.02	1.79§	1.33
	3	1.12§	1.11	1.31	1.18
Acid mists	0	1.00	1.00	1.00	1.00
	1	0.94§	1.05	1.02	1.06
	2	0.95	1.09	0.92	—
	3	1.15§	1.16§	1.50§	1.44§
Insecticides	0	1.00	1.00	1.00	1.00
	1	1.19	1.42	0.58§	0.57§
	2	1.07	1.07		
	3	—	—		
Radiofrequency electromagnetic fields	0	1.00	1.00	1.00	1.00
	1	1.15§	1.16§	1.23§	1.13
	2	0.95	1.03	1.02	0.89
	3	1.14§	1.14§	1.34§	1.33§
Ionizing radiation	0	1.00	1.00	1.00	1.00
	1	0.93	1.07	1.01	1.02
	2	0.96	1.14	1.22	1.56§
	3	0.87§	0.87§	1.02	1.02

* All odds ratios adjusted for age and socioeconomic status (as imputed from occupation).
† For whites and blacks, from Tables 4 and 6.
‡ Calculated after removal of persons with low probability of exposure (level = 1).
§ 95% confidence interval excludes 1.00.

In human MCF-7 breast cancer cells in tissue culture, cadmium has a strong influence on hormone receptor concentration and estrogenic activity.[11]

Ionizing radiation is known to cause breast cancer.[10] Nonionizing electromagnetic radiation has been hypothesized to also increase risk[7]; two studies of male breast cancer support this.[8,9] In this investigation, we found no association with either ionizing or nonionizing radiation.

Estimated exposures to several organic solvents—including carbon tetrachloride, methylene chloride, and formaldehyde—were associated with risk of breast cancer mortality in several analyses. Simultaneous exposure to many solvents is common, and one chemical solvent may serve as a surrogate for exposure to another. Methylene chloride was a common exposure in three breast cancer deaths in a study of aircraft maintenance employees.[13] The literature offers no support for an association of breast cancer risk with formaldehyde exposure.[35]

As suggested by Davis et al,[6] a number of chemicals found in the workplace and general environment can behave as xenoestrogens and modify breast cancer risk by altering estrogen metabolism. Included are some chlorinated organics, PAH, triazine herbicides, and pharmaceuticals. This hypothesis has some epidemiologic support, particularly from the work of Wolff,[36] who showed that sera collected from women who later developed breast cancer had higher levels of DDE than sera from a healthy comparison group. In the current study, we found no association with polychlorinated biphenyls and negative associations with PAHs and with insecticides as a broad exposure class.

In separate analyses of these data that focused on occupational title, we found that jobs high on the SES scale were related to elevated breast cancer mortality risk,[37] an observation made by others.[17,18] At least two factors contributed to this finding. The first is a true underlying association of breast cancer with SES, mediated through reproductive, dietary, or other factors.[17,18] The second is the spurious elevation in observed risk in death certificate case-control studies due to selection of deceased controls from general vital status rosters in which there is an inverse association of SES with probability of death. Most of the exposures reported here are likely to be elevated among lower-paying jobs, so it is not surprising that adjusting for SES increased most risk estimates.

Given the methodologic limitations of this study, it is interesting that we observed associations with several exposures, especially styrene, some organic solvents, metals, and acid mists. These merit further evaluation in investigations in which full occupational histories are available to provide more precise estimates of past exposures.

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